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General review

Segmentation algorithms of subcortical brain structures on MRI for radiotherapy and radiosurgery: A survey

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Abstract

This work covers the current state of the art with regard to approaches to segment subcortical brain structures. A huge range of diverse methods have been presented in the literature during the last decade to segment not only one or a constrained number of structures, but also a complete set of these subcortical regions. Special attention has been paid to atlas based segmentation methods, statistical models and deformable models for this purpose. More recently, the introduction of machine learning techniques, such as artificial neural networks or support vector machines, has helped the researchers to optimize the classification problem. These methods are presented in this work, and their advantages and drawbacks are further discussed. Although these methods have proved to perform well, their use is often limited to those situations where either there are no lesions in the brain or the presence of lesions does not highly vary the brain anatomy. Consequently, the development of segmentation algorithms that can deal with such lesions in the brain and still provide a good performance when segmenting subcortical structures is highly required in practice by some clinical applications, such as radiotherapy or radiosurgery.

1. Introduction

During the last decades, medical imaging, which was initially used for basic visualization and inspection of anatomical structures, has evolved to become an essential tool for diagnosis, treatment and follow-up of patient diseases. Particularly, in oncology, advanced medical imaging techniques are used for tumor resection surgery (i.e. pre-operative planning, intra-operative, post-operative), and for subsequent radiotherapy treatment planning (RTP). Today, brain tumors are the second most common cause of cancer death in men ages 20 to 39 and the fifth most common cause of cancer among women age 20 to 39 [1]. Medical imaging plays a key role in the diagnosis, treatment and follow-up of brain tumors. In daily clinical practice, computed tomography (CT) and magnetic resonance images (MRI) techniques are typically used. Both modalities are complementary: while CT imaging provides bone details MR imaging provides additional information on soft-tissue.

During RTP, the tumor to irradiate, i.e. clinical target volume (CTV), as well as healthy structures to be spared, i.e. the organs at risk (OARs), must be delineated precisely. Because of the high doses used to irradiate the CTV, the risk of severe toxicity of the OARs must be constrained. For the involved OARs some of the tolerance limits are presented in Table 1. Therefore, these segmentations are crucial inputs for the RTP, in order to compute the parameters for the accelerators, and to verify the dose constraints. Nowadays in clinical practice, OARs delineation on medical images is performed manually by experts, or with very few machine assistance [2]. Manual delineation has two major drawbacks: it is time consuming, and achieves poor reproducibility. Typically, the mean time spent to analyze and delineate OAR on a brain MRI dataset has been evaluated to 86 min [3], engaging valuable human resources. Furthermore, the OARs must be interpreted cautiously in light of the observed topological differences, because delineation of structures of in-

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Table 1
Dose limits for the OARs in both radiotherapy and radiosurgery.

Dose level limit (D_{max})		
OAR	Radiotherapy	Radiosurgery
Hippocampus	16 Gy (IMRT – fractionation 10 × 3 Gy) [5]	–
Brainstem	45 Gy (IMRT – fractionation 20 × 1.8 Gy + 10 × (1.8 Gy + 1.6 Gy)) [6]	Volume 1 cc/Dose limit = 10 Gy [7] Volume 1 cc/Dose limit = 12 Gy [8]
Eyes (Retina)	40 Gy (IMRT – fractionation 30 × 2 Gy) [9]	5 Gy [10]
Eyes (Lens)	As low as possible [9]	3 Gy [10]
Cochlea	45 Gy (conventionally fractionated RT) [11]	12 Gy [7], 10 Gy [12]
Chiasma	54 Gy (IMRT – fractionation 30 × 2 Gy) [9]	Volume 0.2CC/Dose limit = 8 Gy [7]
Optic Nerve	54 Gy (IMRT – fractionation 30 × 2 Gy) [9]	Volume 0.2CC/Dose limit = 8 Gy [7,13–15]

terest – CTV and high risked organs – varies considerably from one physician to another [4], showing a poor reproducibility. To overcome these major issues, various computer-aided systems to (semi-)automatically segment anatomical structures in medical images have been developed and published in recent years. However, brain structures (semi-)automatic segmentation still remains challenging, with no general and unique solution.

Initial approaches of brain segmentation on MRI focused on the classification of the brain into three main classes: white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) [16]. During the last two decades, the segmentation of the whole brain into the primary cerebrum tissues (i.e. CSF, GM, and WM) has been one of the core challenges of the neuroimaging community, leading to many publications; nevertheless, it is still an active area of research [17–19]. More recent methods include tumors and adjacent regions, such as necrotic areas [20]. Those methods are only based on signal intensity. However, segmentation of subcortical structures (i.e. OARs) can hardly be achieved based solely on signal intensity, due to the weak visible boundaries and similar intensity values between different subcortical structures. Consequently, additional information, such as prior shape, appearance and expected location, is therefore required to perform the segmentation.

Due to the crucial role of the hippocampus (HC) in learning and memory processes [21] and its role as biomarker for the diagnosis of neural diseases, such as Parkinson, dementia or Alzheimer [22], many methods have been published to (semi-)automatically segment the HC on MRI [23–39]. Although there have recently been some work focusing on other structures than HC, the number of publications related to them is relatively lower. An atlas-based segmentation of the brainstem was validated in radiotherapy [3], demonstrating that the introduction of automatic segmentation methods may be useful in a clinical context. Optic nerves and chiasm were segmented by using a multi-atlas based approach [40]. Lee et al. [41] proposed a 2D automatic segmentation of the brainstem and cerebellum based on active contour models. Segmentation of the corpus callosum has been also investigated by using different methods such as deformable models [42,43], or machine learning [44]. Other researchers have focused on a set of different subcortical and cerebellar brain structures, proposing several approaches: active shape and appearance models [45–50], atlas-based methods [51–56], deformable models [57–59] or machine learning approaches [60–64].

The objective of this article is to provide the reader with a summary of the current state of the art with regard to approaches to segment subcortical brain structures. As it has been reported in the previous section, a large number of techniques have been proposed over the years to segment specific subcortical structures in MRI. However, we are interested in those techniques which are typically applicable to subcortical brain structures in general. In the presented work, we mainly focus on minimally user-interactive methods – automatic or semi-automatic –, which are not tailored to one or few specific structures, but applicable in general. Thus, methods presented in this article can be divided into four main categories: *atlas-based methods, statistical models, deformable models and machine learning methods*.

2. Atlas-based segmentation methods

The transformation of brain MRI segmentation procedures from human expert to fully automatic methods can be witnessed by exploring the atlas-based methods. There are several methods proposed to segment the brain into different anatomical structures using single or multiple atlases. Segmentation by using atlas-based methods can be divided into the following main steps: atlas construction, registration between the atlases and the target image, and optionally atlas selection and label fusion.

2.1. Atlas build-up

First attempts at atlas construction of the human brain were based on a single subject. Here, a single atlas image is used to perform the segmentation [55]. This atlas, referred to as topological, single-subject or deterministic atlas, is usually an image selected from a database to be representative of the dataset to be segmented, in terms of size, shape and intensity for instance. Particularly, for follow-up of patient's disease where segmentation of brain structures should be performed on longitudinal studies (i.e. at different time point along the treatment), the use of single-atlas based segmentation method to propagate segmented structures obtained at one time point to another time point is generally sufficient. However, in applications where no prior image of the patient can be used as atlas, the segmentation using single-atlas based methods of anatomical structures presenting wide variability between humans becomes challenging, and might lead to poor results.

To overcome the limitations encountered with single-atlas based method, multiple atlases can be used [3,30–35,40,51–54]. In this approach, multiple atlas images are selected from a database of images representative of the image to be segmented. Each atlas image is then registered to optimally fit the target image. Subsequently, using the deformation resulting from registration, the atlas labeled image is deformed. At this stage, multiple labeled images are fitted to the target image. At last, propagated labeled images are fused, providing the final segmentation. Beside the registration method used, performance of multi-atlas segmentation methods depends on: 1) the atlas building, 2) the atlas selection (Section 2.3), and 3) the label fusion method (Section 2.4) used. The major drawback of multi-atlas based segmentation methods remains the computation cost since it increases with the number of atlases selected.

A limitation of the multi-atlas based segmentation methods is that individual differences that occur in only a minority of the atlases could be averaged out. Thus, the segmentation results might be biased, particularly for the abnormal MRI scans with pathologies. In order to address this issue, probabilistic atlases are used. This third category of atlases estimates a probabilistic model of the input images, either from a probabilistic atlas or a combination of topological atlases. For a more detailed explanation see the work of Cabezas et al. [65].

2.2. Image registration

Image registration is a prerequisite to perform atlas-based segmentation. The registration process is used to spatially align an atlas A and the target image T. For our segmentation purpose, the registration process involved is necessarily based on non-rigid approaches to tackle inter-individual spatial variation. Various image registration methods exist and have been applied to many medical application domains. We refer the reader to the publications of Hill et al. [66] and Zitova and Flusser [67] for an overview of the image registration methods, regardless of particular application areas. A review of image registration approaches specifically used in brain imaging is available in the publication of Toga and Thompson [68]. The main contributions, advantages, and drawbacks of existing image registration methods are addressed.

2.3. Atlas selection

Normal individual variations in human brain structures present a significant challenge for atlas selection. Some studies demonstrated that, although the use of more than only one topological atlas improves the accuracy of the segmentation, it is not necessary to use all the cases in a dataset for a given query image [32,35,52,53,55,69,70]. Among the existing solutions to choose the best matching cases, the use of meta-information is the simplest case. In this solution, which can be also called population specific atlases, an average atlas is built for several population groups according to similar features, like gender or age. Although they represent the simplest solution, the use of meta-information has proved to be a powerful similarity criterion when used in multi-atlas segmentation [52]. However, this information may not be always available, requiring the use of similarity metrics to compare both atlas and target image.

Initially, the majority of published works used a single individual image randomly selected from the atlas dataset, where the selection criterion was not even mentioned. The optimal selection of a single template from the entire dataset during atlas-based segmentation and its influence in the segmentation accuracy was investigated in [69]. Han et al. [70] compared the selection of a single atlas against the propagation and fusion of their entire atlas database. In their work, the selection of the single atlas was based on the highest Mutual Information (MI) similarity between atlases and the target image after a global affine registration. Multi-atlas segmentation strategy significantly improved the accuracy of single-atlas based strategy, especially in those regions which represented higher dissimilarities between images. Additionally to MI, Sum of squared differences (SSD) or cross-correlation (CC) are often used as a similarity metric to select the closest atlas with respect to the target image.

Aljabar et al. [52] proved that using multi-atlas selection when segmenting subcortical brain structures improves the overlapping than when using random sets of atlases. In their work, a dataset of 275 atlases was used. As in [70], MI similarity was used to top-rank the atlases from the dataset. Then, the n top ranked atlases from the list were selected to be propagated to the target image by using a non-rigid registration. Mean DSC obtained by selecting the top-ranked atlases (0.854) was higher than the DSC obtained randomly selecting the atlases (0.811). This difference represents nearly 4% of improvement, demonstrating that the selection of a limited number of atlases which are more appropriate for the target image and prior to multi-atlas segmentation, would appear preferable to the fusion of an arbitrarily large number of atlases.

The inclusion in the label propagation step of atlases containing high dissimilarities with respect to the target image, may not make the segmentation more accurate, but contribute to a poorer result. Consequently, the proper selection of the atlases to include in the label propagation is a key step of the segmentation process.

2.4. Label fusion

Once the suitable atlases have been selected from the atlas dataset and labels propagated to the target image, information from transferred labels has to be combined to provide the final segmentation [30–36,40,51,52,54,69,71,72]. This step is commonly referred as label fusion or classifier fusion.

Label fusion techniques known as best atlas and majority voting approach represent the simplest strategies to combine the propagated labels. In best atlas technique, after the registration step, the labels from the most similar atlas to the target image are propagated to yield the final segmentation. In majority voting method, votes for each propagated label are counted and the label receiving the most votes is chosen to produce the final segmentation [31,51,52]. Since majority voting assigns equal weights to different atlases, it makes a strong assumption that

different atlases produce equally accurate segmentations for the target image.

To improve label fusion performance, recent work focuses on developing segmentation quality estimations based on local appearance similarity and assigning weights to the propagated labels. Thus, final segmentation is obtained by increasing the contribution of the atlases that are more similar to the target scan [30–35,55,69]. Among previous weighted voting strategies, those that derive weights from local similarity between the atlas and target [30,32–34], and thus allow the weights to vary spatially, have demonstrated to be a better solution in practice. Hence, each atlas contributes to the final solution according to how similar to the target they are. However, the computation of the weights is done independently for each atlas, and the fact that different atlases may produce similar label errors is not taken into account. This assumption can lead to labeling inaccuracies caused by replication or redundancy in the atlas dataset. To address this limitation, a solution for the label fusion problem was proposed [35]. In this work the weighted voting was formulated in terms of minimizing the total expectation of labeling error and the pairwise dependency between atlases was explicitly modeled as the joint probability of two atlases making a segmentation error at a voxel. Hence, the dependencies among the atlases were taken into consideration, and the expected label error was reduced in the combined solution.

Another remarkable example of producing consensus segmentations, especially in the context of medical image processing, is the algorithm named Simultaneous Truth and Performance Level Estimation (STAPLE) [71]. STAPLE approach, instead of using an image similarity metric to derive the classifier performance, estimates the classifier performance parameters by comparing each classifier to a consensus, in an iterative manner according to the Expectation Maximization (EM) algorithm. In order to model miss registrations as part of the rater performance, a reformulation of STAPLE with a spatially varying rater performance model was introduced [72]. More recently, Cardoso et al. [36] extended the classical STAPLE approach by incorporating a spatially image similarity term into a STAPLE framework, enabling the characterization of both image similarity and human rater performance in a unified manner, which was called Similarity and Truth Estimation for Propagated Segmentations (STEPS). At last, a novel reformulation of the STAPLE framework from a non-local perspective, called Non-local Spatial STAPLE [54], was used as a label fusion algorithm [40].

3. Statistical models

Statistical models (SM) have become widely used in the field of computer vision and medical image segmentation over the past decade [26,45–50,73–88]. Basically, SMs use a priori shape information to learn the variation from a suitably annotated training set, and constrain the search space to only plausible instances defined by the trained model. The basic procedure of SM – of shape and/or texture – is as follows: 1) the vertices (control points) of a structure are modeled as a multivariate Gaussian distribution; 2) shape and texture are then parameterized in terms of the mean and eigenvectors of both the vertex coordinates and texture appearance; 3) new instances are constrained to a subspace of allowable shapes and textures, which are defined by the eigenvectors and their modes of variation. Consequentially, if the dimensionality of the shape representation exceeds the size of the training data, the only permissible shapes and textures are linear combinations of the original training data.

3.1. Training phase. Construction of the statistical model

3.1.1. Modeling the shape

Statistical shape model (SSM) construction basically consists in extracting the mean shape and a number of modes of variation from a collection of training samples to represent the possible shapes that the model is able to generate. Landmarks based method is a generic technique coined as Point Distribution Models (PDMs) by Cootes et al. [74], which has been extensively used in SSMs for surface representation. This method regularly distributes a set of points across the surface, which usually relies on high curvatures of boundaries. However, they do not need to be placed at salient feature points as per the common definition of anatomical landmark, which is the reason why they have also been referred to as semi-landmarks. Among other shape representation models that have been recently used in medical image segmentation [73] we can identify medial models or skeletons, meshes, vibration modes of spherical meshes or the use of wavelets, for example.

Alignment of the training shape samples in a common coordinate frame is the first step to create the shape model. Once the samples are co-registered, a reduced number of modes of variation that best describes the variation observed are extracted, which is usually done by applying Principal Components Analysis (PCA) to the set of vectors describing the shapes [75]. PCA picks out the main axes of the cloud, and models only the first few, which account for the majority of the variation. Thus, any new instance of the shape can be modeled by the mean shape of the object and a combination of its modes of variations [74].

3.1.2. Modeling the appearance

As an extension of the statistical models of shape, the texture variability observed in the training set was included in the model, leading to appearance models (AMs) [76]. In this approach, in addition to the shape, the intensity variation seen in the training set is also modeled. As in the SSM, the variability observed in the training set is parameterized in terms of its mean and eigenvectors. Once the shape has been modeled (see Section 3.1.1), the statistical model of the gray level appearance has to be built. For this purpose, sample images are warped based on the mean shape. Then, the intensity information from the shape-normalized image is sampled over the region covered by the mean shape. Different techniques to sample the intensity in the warped image can be found in the literature [73].

3.2. Segmentation phase. Search algorithm

Once the SM has been created, it is important to define the strategy to search new instances of the model in the input images. This step consists essentially in finding the most accurate parameters of the statistical model that best define a new object. Active shape models (ASM) and active appearance models (AAM) are the most frequently employed constrained search approaches and are described below.

3.2.1. Active shape model

Originally introduced by Cootes et al. [74,75], ASM is a successful technique to find shapes with known prior variability in input images. ASM has been widely used for segmentation in medical imaging [73], including segmentation of subcortical structures on brain [47,48,77–84]. It is based on a statistical shape model (SSM) to constrain the detected organ boundary to plausible shapes (i.e. shapes similar to those in the training data set). Given a coarse object initialization, an instance of the model can be fit to the input image by selecting a set of shape parameters defined in the training phase (see Section 3.1.1).

Original ASM method [75] was improved in [77] by using an adaptive gray-level AM based on local image features around the border of the object. Thus, landmarks points could be moved to better locations during the optimization process. To allow some relaxation in the shape instances fitted by the model, ASM can be combined with other methods, as in [79]. They employed a framework involving deformable templates constrained by statistical models and other expert prior knowledge. This approach was used to segment four brain structures: corpus callosum, ventricles, hippocampus and caudate nuclei. Most of the ASMs used in the literature are based on the assumption that the organs to segment are usually located on strong edges, which may lead to a final shape far from the actual shape model. Instead, [83] presented a novel method which was based on the combined use of ASM and Local Binary Patterns (LBP) as features for local appearance representations to segment the midbrain. In this way, segmentation performance was improved with respect to the ASM algorithm.

A major limitation of ASM is the size of the training set (especially in 3D), due to lack of representative data and time needed for model construction process. Hence, 3D ASMs tend to be restrictive in regard to the range of allowable shapes, over-constraining the deformation. Zhao et al. [80] overcame this limitation by using a partitioned representation of the ASM where, given a PDM, the mean mesh was partitioned into a group of small tiles, which were used to create the statistical model by applying the PCA over them. Other techniques focus on artificially enlarging the size of the training set. Koikkalainen et al. [85] concluded that the two best enlargement techniques were the non-rigid movement technique and the technique that combines PCA and a finite element model.

3.2.2. Active appearance model

The active appearance model (AAM) is an extension of the ASM that, apart from the shape, models both the appearance and the relationship between shape and appearance of the object [76]. Since the purpose of this review is to give a view about the use of these methods in medical image segmentation (especially of the subcortical structures on MRI), and not to enter into detail in the mathematical foundations of each methods, we encourage the readers to review a detailed description of the algorithm in [76].

Initially, Cootes et al. [49] demonstrated the application of 2D AAMs on finding structures in brain MR images. Nevertheless, they are not suitable for 3D images in their primary form because of the underlying shape representation (i.e. PDM) that becomes impractical in 3D. Some approaches extended them to higher dimension by using non-linear registration algorithms for the automatic creation of a 3D-AAM. Duchesne et al. [45] segmented medial temporal lobe structures by including non-linear registration vector fields into a 3D warp distribution model.

However, a number of considerations have to be taken into account in adapting a generic AAM approach to a specific task. Babalola et al. [86] built AAMs of some subcortical structures using groupwise registration to establish correspondences, i.e. to initialize the composite model within the new image. To build the AAMs, the intensities along vectors normal to the surface of the structures were sampled, which is known as profile AAM. In [50], the proposed approach used a global AAM to find an approximate position of all the structures in the brain. Once the coarse localization was found, shape and location of each structure were refined by using a set of AAMs individually trained for each of the structures. Although the probability of object occupancy could be derived from the training set, they demonstrated that the use of simple regressors at each voxel based on the pattern of gray level intensities nearby provided better results.

3.2.3. Initialization

Most of the methods that aim to locate a SSM in a new input image use a local search optimization process. So, they need to be initialized near the structure of interest, so that the model boundaries fall in the close vicinity of object boundaries in the image. Straightforward solution for the initialization problem is human-interaction. In some cases, it is sufficient to roughly align the mean shape with the input data, whereas in other cases, it is preferred to use a small number of points to guide the segmentation process [77]. Alternatively, more robust techniques can be used to initialize the model in the image [86–88].

4. Deformable models

The term “deformable model” (DM) was pioneered by Terzopoulos et al. [89] to refer to curves or surfaces, defined in the image domain, and which are deformed under the influence of internal and external forces. Internal forces are related with the curve features and try to keep the model smooth during the deformation process. On the other hand, external forces are responsible of attracting the model toward features of the structure of interest, and are related with the image features of the adjacent regions to the curve. Hence, DM tackles the segmentation problem by considering an object boundary as a single,

connected structure, and exploiting a priori knowledge of object shape and inherent smoothness [89]. Although DM were originally developed to provide solutions for computer vision applications to natural scenes and computer graphics problems, their applicability in medical image segmentation has already been proven [90].

According to the type of shape representation used to define the model, DM methods can be categorized in: parametric or explicit deformable models [23,41,42,57,91,92] and geometric or implicit deformable models [27,37,43,58,59,93–98].

4.1. Parametric deformable models

The first parametric model used in image segmentation found in the literature was originally introduced by Kass et al. [91], coined with the name of "snakes". It was proposed as an interactive method where, because of its limitations, initial contours must be placed within the vicinity of object boundaries. First, the energy of the contour depends on its spatial positioning and changes along the shape. Sensitivity to initial location obliges the contour to be placed close to the object boundary, leading to failure in case of improper initialization. Second, the presence of noise may cause the contour to be attracted by a local minimum and get stuck in a location that might not correspond with the ground truth. To overcome these limitations different approaches have been proposed [90,92]. The method presented in [92] provides different mechanisms to enable the contour topology to change during the deformation process. In [90], an extensive study of DM and different types of external forces was presented.

Regarding the segmentation of subcortical structures, parametric DM have been recently employed to perform the segmentation, in combination with other approaches [23,41,42,57]. Additionally to the anatomical priors derived from retrieved landmarks, a probabilistic priors derived from an atlas was used to drive the proposed approach in [23] to segment simultaneously the HC and the amygdala. Ada-boosted algorithm was used in [41] to detect brainstem and cerebellum candidate areas, followed by an active contour model to provide the final boundaries. In [42], the application of genetic algorithms to DM was explored in the task of corpus callosum segmentation. In this approach, genetic algorithms were proposed to reduce typical deformable model weaknesses pertaining to model initialization, pose estimation and local minima, through the simultaneous evolution of a large number of models. An extension of natural snakes was proposed in [57], where desired properties of physical models were combined with Fourier parameterizations of shapes representations and their shape variability to segment the corpus callosum.

4.2. Geometric deformable models

One of the main drawbacks of parametric DM is the difficulty of naturally handling topological changes for the splitting and merging of contours, restricting severely the degree of topological adaptability of the model. To introduce topological flexibility, geometric DM have been implicitly implemented by using the level set (LS) algorithm developed by Osher and Sethian [93]. These models are formulated as evolving contours or surfaces, usually called fronts, which define the LS of some higher-dimensional surface over the image domain.

Generally, image gray level based methods face difficult challenges such as poor image contrast, noise, and diffuse or even missing boundaries, especially for certain subcortical structures. In most of these situations, the use of prior model based algorithms can solve these issues. The method proposed in [94] used a systematic approach to determine a boundary of an object as well as the correspondence of boundary points to a model by constructing a statistical model of shape variation. Ghanei et al. [37] used a deformable contour technique to customize a balloon model to the subjects' hippocampus. In order to avoid local minima due to mismatches between model edge and multiple edges in the image, their technique incorporates statistical information about the possible range of allowable shapes for a given structure. Geodesic active contours were extended in [43] by incorporating shape information into the evolution process. PCA and LS functions of the object boundaries were employed to form a statistical shape model from a training set. The segmenting curves evolved according to image gradients and a maximum a posteriori (MAP) estimated the shape and pose.

Additionally, the use of LS methods to formulate the segmentation problem has been reported to increase the capture range of DM and constrain the deformation through the incorporation of some prior shape information. Mesejo et al. [98] presented a segmentation approach based on the LS method, called HybridLS, that combined edge, region and prior shape knowledge of the target object to guide the LS evolution. Because of these advantages geometric DMs have been extensively used to carry out the segmentation task of brain subcortical structures [37,43,58,59,94–98].

In some situations, texture information is also required to constrain the deformation on the contours. As a consequence, statistical models of both shape and texture are used in addition to only shape prior based segmentation methods [49,76]. The modeled structure can be located by finding the parameters, which minimize the difference between the synthesized model image and the target image in conjunction with the statistical model of the shape based on landmark points and texture.

5. Machine learning methods

Machine Learning (ML) techniques have been extensively used in the MRI analysis domain almost since its creation. Artificial Neural Networks (ANN), or Support Vector Machines (SVM), are among the most popular methods used not only for segmentation of brain anatomical structures [25,38,39,44,60–64,99–102], but also for tumors classification [103–105] or automatic diagnosis [106].

5.1. Artificial neural networks

An artificial neural network (ANN) represents an information processing system containing a large number of intercon-

nected individual processing components, i.e. neurons. Motivated by the way the human brain processes input information, neurons work together in a distributed manner inside each network to learn from the input knowledge, process such information and generate a meaningful response. Each neuron n inside the network processes the input through the use of its own weight w_n, a bias value b_n, and a transfer function which takes the sum of w_n and b_n. Depending on the transfer function selected and the way the neurons are connected, distinct neural networks can be constructed.

Because of their efficacy in solving optimization problems, ANN have been integrated in segmentation algorithms to define subcortical structures [25,60–62,99,100]. In the method proposed in [25], gray-level dilated and eroded versions of the MR T1 and T2-weighted images were used to minimize leaking from the HC to surrounding tissue combined with possible foreground tissue. An ANN was applied to a manually selected bounding box, which result was used as an initial segmentation and then used as input of the gray-level morphology-based algorithm. Magnotta et al. [60] used a three-layer ANN to segment caudate, putamen and whole brain. The ANN was trained using a standard back-propagation algorithm and a piecewise linear registration was used to define an atlas space to generate a probability map which was used as input feature of the ANN. This approach was later employed by [99] and extended by [62] through the incorporation of a landmark registration to segment the cerebellar regions. Based on the success of applying ANN approaches to segment cerebellar regions by incorporating a higher dimensional transformation, Powel et al. [61] extended the initial algorithm of [60] to use a high dimensional intensity-based transform. Further, they compared the use of ANN with SVM, as well as with more classical approaches such as single-atlas segmentation and probability based segmentation. In [100], a two-stage method to segment brain structures was presented, where geometric moment invariants (GMI) were used to improve the differentiation between the brain regions. In the first stage, GMI were used along voxel intensity values as an input feature and a signed distance function of a desired structure as an output of the network. To represent the brain structures, the GMI were employed in 8 different scales, using one ANN for each of the scales. In the second stage, the network was employed as a classifier and not as a function approximator.

Some limitations must be taken into account when ANN are employed. Their performance strongly depends on the training set, achieving good results only in those structures for which a suitable training can be developed. This may limit their value with inherently difficult structures that human beings have difficulty delineating reliably, such as the thalamus [60]. As a consequence, ANN must be well designed, and different types of ANN may require specific training data set development, depending on the structure-identification task.

5.2. Support vector machine

Support vector machine represent one of the latest and most successful statistical pattern classifiers. It has received a lot of attention from the machine learning and pattern recognition community. Although SVM approaches have been mainly employed for brain tumor recognition [104,105] in the field of medical image classification, recent works have also used them for tissue classification [101] and segmentation of anatomical human brain structures [38,39,44,61,63,64,102].

The main idea behind SVM is to find the largest margin hyperplane that separates two classes. The minimal distance from the separating hyperplane to the closest training example is called margin. Thus, the optimal hyperplane is the one showing the maximal margin, which represents the largest separation between the classes. The training samples that lie on the margin are referred as support vectors, and conceptually are the most difficult data points to classify. Therefore, support vectors define the location of the separating hyperplane, being located at the boundary of their respective classes.

The growing interest on SVM for classification problems lies in its good generalization ability and its capability to successfully classify non-linearly separable data. First, SVM attempts to maximize the separation margin – i.e., hyperplane – between classes, so the generalization performance does not drop significantly even when the training data are limited. Second, by employing kernel transformations to map the objects from their original space into a higher dimensional feature space [107], SVM can separate objects which are not linearly separable. Moreover, they can accurately combine many features to find the optimal hyperplane. Hence, as can be seen, SVM globally and explicitly maximize the margin while minimizing the number of wrongly classified examples, using any desired linear or non-linear hypersurface.

Powell et al. [61] compared the performance of ANN and SVM when segmenting subcortical (caudate, putamen, thalamus and hippocampus) and cerebellar brain structures. In their study the same input vector was used in both machine learning approaches, which was composed by the following features: probability information, spherical coordinates, area iris values, and signal intensity along the image gradient. Although results obtained where very similar, ANN based segmentation approach slightly outperformed SVM. However, their employed a reduced number of brains to test (only 5 brains), and 25 manually selected features, which means that generalization to other datasets was not guarantee. PCA was used in [63] to reduce the size of the input training pool, followed by a SVM classification to identify statistical differences in the hippocampus. In addition, Dolz et al. [44] explored the use of SVM to segment the corpus callosum. In this work, additionally to the input features used in [61], geodesic image transform map was added as input vector of the SVM. Segmentation of internal caudate nuclei by SVM was proposed in [64]. In their work, an alternative method based on the extraction of an extended set of shape features describing the caudate region for each slice and their classification using SVM was presented. However, selection of proper discriminative features is not a trivial task, which has already been explored in the SVM domain. To overcome this problem, AdaBoost algorithm was combined with a SVM formulation [39]. AdaBoost was used in a first stage to select the features that most accurately span the classification problem. Then, SVM

fused the selected features together to create the final classificatory. Furthermore, they compared four automated methods for hippocampal segmentation using different machine learning algorithms: hierarchical AdaBoost, SVM with manual feature selection, hierarchical SVM with automated feature selection (Ada-SVM), and a publicly available brain segmentation package (FreeSurfer). In their proposed study, they evaluated the benefits of combining AdaBoost and SVM approaches sequentially.

6. Discussion

Generally, none of the presented methods can singly handle brain subcortical structures segmentation with the presence of brain lesions. Typically, methods discussed in this survey rely on the existent information in a training set. However, subjects presenting brain lesions are not usually representative for a large set of patients, because of lesions may strongly differ and produce random deformations on the subcortical structures. As a consequence, they are not included in the training stage and the deformations on the structures caused by the lesion cannot be therefore modeled.

Model based approaches, such as atlas or statistical models trend to perform reasonably well when there is no high anatomical deviation between the training set and the input case to analyze. Nevertheless, these approaches might completely fail if shape variability is not properly modeled, which often occurs in the presence of brain lesions. Additionally to the shape variability, registration plays an important role in atlas-based approaches. Registrations with large initial dissimilarity in shape between the atlases and the target might not be handled properly. This can lead to inappropriately weights when there are initially large shapes differences resulting in incorrect image correspondences established by the atlas registration. In the other hand, in statistical model approaches, which are only capable of generating a plausible range of shapes, the presence of a tumor might deform a determined structure to an unpredictable shape. This will cause the failure of SM approaches, because of their incapability to generate new unknown shapes which considerably differs from the shapes in the training set.

In the context of SMs, PCA was originally used in a framework called Active Shape Model (ASM) [75] and has become a standard technique used for shape analysis in segmentation tasks, and the preferred methodology when trying to fit a model into new image data. Compared to ASM, AAM makes an excessive usage of the memory when it creates the 3D texture model, and the implementation of ASM is relatively easier than the AAM implementation. While ASMs search around the current location and along profiles, AAMs only examine the image under its current area of interest, allowing the ASMs to generally have a larger capture range. However, the use of information solely around the model points makes that ASMs may be less reliable, since they do not profit from all texture information available across a structure, unlike AAM. Another interest advantage of the AAMs reported by [49] is related with the number of landmarks required to build a statistical model. Compared to the ASMs, AAMs can build a convincing model with a relatively small number of landmarks, since any extra shape variation may be encoded by additional modes of the texture model. Consequently, although the ASM is faster and achieves more accurate feature point location than the AAM, the AAM gives a better match to the image texture, due to it explicitly minimizes texture errors. Furthermore, ASM is less powerful in detecting the global minima and may converge to a local minimum due to multiple nearby edges in the image. These situations make AAM usually more robust than ASM. Although the main advantage of using PCA in SMs is to constraint the segmentation task to the space spanned by the eigenvectors and their modes of variation, it has two major limitations. First, the deformable shapes that can be modeled are often very restricted. Secondly, finer local variations of the shape model are not usually encoded in these eigenvectors. Consequently, new instances containing these small variations will not be properly fitted in the model instance.

Contrary to statistical models, DM provide flexibility and do not require explicit training, though they are sensitive to initialization and noise. SMs may lead to greater robustness, however they are more rigid than DM and may be over-constrained, not generalizing well to the unsampled population, particularly for small amounts of training data relative to the dimensionality. This situation can appear on new input examples with pathologies, lesions or presenting high variance, different from the training set. Models having local priors similar to DM formulation do not have this problem. They will easily deform to highly complex shapes found in the unseen image. Hence, many methods attempt to find a balance between the flexibility of the DM and the strict shape constraints of the SM by fusing learnt shape constraints with the deformable model.

Notwithstanding, some main limitations have to be taken into account when working with generic parametric DM. First, if the stopping criterion is not defined properly, or boundaries of the structures are noisy, DM may get stuck in a local minimum which does not correspond to the desired boundary. Second, in situations where the initial model and the desired object boundary differ greatly in size and shape, the model must be reparameterized dynamically to faithfully recover the object boundary. Methods for reparameterization in 2D are usually straightforward and require moderate computational overhead. However, reparameterization in 3D requires complicated and computationally expensive methods. Further, it has difficulties when dealing with topological adaptation, caused by the fact that a new parameterization must be constructed whenever the topology change occurs, which may require sophisticated schemes. This issue can be overcome by using LSs. Moreover, as DM represent a local search, they must be initialized near the structure of interest.

By introducing machine learning methods, algorithms developed for medical image processing often become more intelligent than conventional techniques. Improvements in the resulting relative overlaps came from the application of the machine learning methods including ANN and SVM [61]. A comparison done in this work between four methods (template based, probabilistic atlas, ANN and SVM) showed that machine learning

Table 2
Summary of all methods presented to segment OARs in brain cancer. Part I.

Method	Ref.	Structures	Image modalities
Single atlas-based	Kwak [28]	Hippocampus	MR T1
	Wu [55]	Multi-structure	MR T1
Multi atlas based	Bondiau [3]	Brainstem	MR T1, T2
	Al Shaikhli [56]	Brainstem, cerebellum, ventricles	MR T1
Multiple atlas-based	Zarpalas [29]	Hippocampus	MR T1
	Artaechevarria [30]	Multi-structure	MR
	Collins [31]	Hippocampus, amygdala	MR T1
	Khan [32]	Hippocampus	MR T1
	Kim [33]	Hippocampus	MR 7T
	Coupé [34]	Multi-structure	MR T1
	Wang [35]	Hippocampus	MR
	Cardoso [36]	Hippocampus	MR T1
	Panda [40]	Optic nerve, eye globe	CT
	Heckemann [51]	Multi-structure	MR T1
	Aljabar [52]	Multi-structure	MR T1
	Lötjönen [53]	Multi-structure	MR T1
	Asman [54]	Multi-structure	MR
Active shape models	Bailleul [47]	Multi-structure	MR
	Tu [48]	Multi-structure	MR T1
	Pitiot [79]	Multi-structure	MR T1
	Zhao [80]	Multi-structure	MR
	Rao [81]	Multi-structure	MR
	Bernard [82]	Subthalamic nucleus	MR T1
	Olveres [83]	Mid brain	MR T1, SWI
Active appearance models	Hu [26]	Hippocampus, amygdala	MR T1, T2
	Duchesne [45]	Medial temporal lobe	MR T1
	Hu [46]	Medial temporal lobe	MR T1
	Cootes [49]	Multi-structure	MR
	Brejl [78]	Corpus callosum, cerebellum	MR
	Babalola [50,86]	Multi-structure	MR T1
Parametric deformable models	Lee [41]	Brainstem, cerebellum	MR
	McIntosh [42]	Corpus callosum	MR
	Szekely [57]	Multi-structure	MR
	McInerney [92]	Corpus callosum, cerebellum	MR
Geometric deformable models	Shen [24]	Hippocampus	MR T1
	Zhao [27]	Hippocampus	MR
	Ghanei [37]	Hippocampus	MR
	Leventon [43]	Corpus callosum	MR
	Yang [58]	Multi-structure	MR
	Tsai [59]	Ventricle, caudate nuclei, lenticular nucleus	MR
	Wang [94]	Corpus callosum, basal ganglia, ventricle boundaries	MR
	Duncan [95]	Hippocampus	MR T1
	Bekes [96]	Eyeballs, lens, nerves	CT
Machine learning. ANN	Hult [25]	Hippocampus	MR T1, T2
	Magnotta [60]	Corpus callosum, putamen, caudate nuclei	MR T1, T2
	Powell [61]	Multi-structure	MR T1, T2, PD
	Pierson [62]	Cerebellar subregions	MR T1, T2
	Spinks [99]	Thalamus, mediodorsal nucleus	MR T1, T2, PD
	Moghaddam [100]	Putamen, caudate, thalamus	MR T1
Machine learning. SVM	Morra [38,39]	Hippocampus	MR T1
	Dolz [44]	Corpus callosum	MR T1
	Powell [61]	Multi-structure	MR T1, T2, PD
	Golland [63]	Hippocampus, amygdala, corpus callosum	MR

algorithms outperformed the template and probabilistic-based methods when comparing the relative overlap. There was also little disparity between the ANN and SVM based segmentation algorithms. ANN training took significantly longer than SVM training but can be applied more quickly to segment the regions of interest. It was reported that it took a day to train an ANN for the classification of only one structure from the others even though a random sampled data was used instead of the whole

Table 3
Summary of benefits, assumptions and limitations of different segmentation methods for brain structures.

Method	Benefits	Assumptions and/or limitations
Single atlas-based	– Fast – Sufficient for intra-patient segmentation	– Lower accuracy if there is significant anatomical variation
Multiple atlas-based	– Capable to cover a higher variability than with a single atlas – Combination of propagated labels may overcome limitations of single atlases – Atlases are easy to build	– Computationally expensive – Rely on the registration – Success also depends on atlas building
Active shape models	– Relatively fast – Easy to implement – Larger capture range than AAM – Robust against noise	– Cannot create unseen shapes – Not robust when different images are introduced – May not converge to a good solution
Active appearance models	– More powerful than ASM in detecting the global minima – Better match to image texture than ASM – Robust against noise	– Excessive usage of memory – Hard to implement – Cannot generalize well to unsampled population
Parametric deformable models	– No training required – Provide flexibility	– Sensitive to initialization – Susceptible to noise and artifacts
Geometric deformable models	– No training required – Provide flexibility – Ability to handle topological changes – Easily deform to highly complex structures	– Sensitive to initialization – Stopping criteria hard to define – May get stuck in any local minima
Artificial neural networks	– Can be used for classification or regression – Able to represent Boolean functions – Tolerant of noisy inputs – Instances can be classified by more than one output	– Difficult to understand structure of the algorithm – Too many attributes can result in overfitting – Optimal network structure can only be determined by experimentation
Support vector machines	– Models non-linear class boundaries – Overfitting is unlikely to occur – Computational complexity reduced to quadratic optimization problem – Easy to control complexity of decision rule and frequency of error	– Training is slow compared to other ML approaches – Difficult to determine optimal parameters when training data is not linearly separable – Difficult to understand structure of the algorithm

dataset. While machine learning methods are undoubtedly powerful tools for classification and pattern recognition, there are potential disadvantages when applying them to a given problem. Machine learning approaches, in general, are notoriously hard to interpret and analyze, and in situations where it is desirable to simply and concisely define the process transforming inputs to output values it can be difficult to justify their use. (See Tables 2 and 3 for a complete overview of presented approaches.)

However, despite the large number of presented techniques to perform automatic segmentation of brain subcortical structures, it still remains challenging, especially when lesions, such as tumors, are present. The presence of lesions in the brain might compress some of the subcortical areas, making these deformations hard to model by some of the presented methods. Thus, the main challenge lies in the segmentation of subcortical structures with anatomical deviation caused by the presence of tumor with different shape, size, location and intensities. The tumor not only changes the part of the brain where tumor exists, but also sometimes influences shape and intensities of other structures of the brain. Thus, the existence of such anatomical deviation makes use of prior information about intensity and spatial distribution challenging.

7. Conclusion

Four approaches applicable to the (semi-)automatic segmentation of subcortical brain structures in general have been presented in this work. In spite of the availability of a large variety of state-of-art methods for subcortical brain structures segmentation on MRI, we may conclude that there is a gap missing in such state-of-the-art, as no subcortical structures segmentation methods with presence of tumors seem to have been fully explored yet.

The development of segmentation algorithms that can deal with such lesions in the brain and still provide a good performance when segmenting subcortical structures is highly required in practice by some clinical applications, such as radiotherapy or radiosurgery.

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